

TRANSMITTAL FORM

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Application Number	09/970,020
Filing Date	10/03/2001
First Named Inventor	Liu et al.
Art Unit	1615
Examiner Name	R. Joynes
Attorney Docket Number	107223.139
Total Number of Pages in This Submission	53

ENCLOSURES (Check all that apply)

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Firm or Individual name	Emily R. Whelan, Reg. No. 50,391
Signature	<i>Emily R Whelan</i>
Date	12/16/2003

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Effective 10/01/2003. Patent fees are subject to annual revision.

☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT (\$) 165.00

Complete if Known

Application Number	09/970,020
Filing Dat	10/03/2001
First Named Inventor	Liu et al.
Examiner Name	R. Joynes
Art Unit	1615
Attorney Docket No.	107223.139

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account:

Deposit
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08-0219

Hale and Dorr LLP

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description	Fee Paid
1001 770	2001 385	Utility filing fee	
1002 340	2002 170	Design filing fee	
1003 530	2003 265	Plant filing fee	
1004 770	2004 385	Reissue filing fee	
1005 160	2005 80	Provisional filing fee	
SUBTOTAL (1)			(\$) 0.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims	Fee from below	Fee Paid
Total Claims	-20** =	X	
Independent Claims	-3** =	X	
Multiple Dependent		0	0

Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description
1202 18	2202 9	Claims in excess of 20
1201 86	2201 43	Independent claims in excess of 3
1203 290	2203 145	Multiple dependent claim, if not paid
1204 86	2204 43	** Reissue independent claims over original patent
1205 18	2205 9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) (\$) 0.00

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Small Entity

Fee Code (\$)	Fee Code (\$)	Fee Description	Fee Paid
1051 130	2051 65	Surcharge - late filing fee or oath	
1052 50	2052 25	Surcharge - late provisional filing fee or cover sheet	
1053 130	1053 130	Non-English specification	
1812 2,520	1812 2,520	For filing a request for ex parte reexamination	
1804 920*	1804 920*	Requesting publication of SIR prior to Examiner action	
1805 1,840*	1805 1,840*	Requesting publication of SIR after Examiner action	
1251 110	2251 55	Extension for reply within first month	
1252 420	2252 210	Extension for reply within second month	
1253 950	2253 475	Extension for reply within third month	
1254 1,480	2254 740	Extension for reply within fourth month	
1255 2,010	2255 1,005	Extension for reply within fifth month	
1401 330	2401 165	Notice of Appeal	
1402 330	2402 165	Filing a brief in support of an appeal	165.00
1403 290	2403 145	Request for oral hearing	
1451 1,510	1451 1,510	Petition to institute a public use proceeding	
1452 110	2452 55	Petition to revive - unavoidable	
1453 1,330	2453 665	Petition to revive - unintentional	
1501 1,330	2501 665	Utility issue fee (or reissue)	
1502 480	2502 240	Design issue fee	
1503 640	2503 320	Plant issue fee	
1460 130	1460 130	Petitions to the Commissioner	
1807 50	1807 50	Processing fee under 37 CFR 1.17(q)	
1806 180	1806 180	Submission of Information Disclosure Stmt	
8021 40	8021 40	Recording each patent assignment per property (times number of properties)	
1809 770	2809 385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810 770	2810 385	For each additional invention to be examined (37 CFR 1.129(b))	
1801 770	2801 385	Request for Continued Examination (RCE)	
1802 900	1802 900	Request for expedited examination of a design application	

Other fee (specify)

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) (\$) 165.00

SUBMITTED BY

(Complete if applicable)

Name (Print/Type)	Emily R. Whelan	Registration No. (Attorney/Agent)	50,391	Telephone	617-526-6567
Signature	Emily R. Whelan	Date	12/16/2003		

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PATENT

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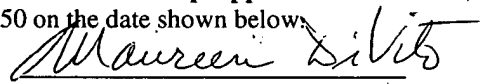
Applicant:	Liu et al.)	Examiner:	R. Joynes
)		
Serial No.:	09/970,020)	Art Unit:	1615
)		
Filed:	October 3, 2001)	Confirmation No.:	8697
)		
Entitled:	Developing A Delivery System)	Atty. Docket No.:	107223-139 US
	For Multi-Pharmaceutical Active)		
	Materials at Various Release Rates)		

CERTIFICATION UNDER 37 C.F.R. § 1.10

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Maureen DiVito

APPEAL BRIEF UNDER 37 C.F.R. § 1.192

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Sir:

This is an Appeal Brief pursuant to the Notice of Appeal filed on October 23, 2003, appealing the rejection of claims 24-54 in the Final Office Action of July 24, 2003. This Brief is being filed in triplicate.

I. REAL PARTY IN INTEREST

The real party in interest is Penwest Pharmaceuticals Co., the assignee of the present application.

II. RELATED APPEALS AND INTERFERENCES

The Appellants, the Appellants' legal representatives, and the Assignee are not aware of any pending appeal or interference that would directly affect, be directly affected by, or have a bearing on the Board's decision in this appeal.

III. STATUS OF THE CLAIMS

Claims 24-54 are pending in the application, and are finally rejected. Claims 1-23 were canceled during prosecution. Claims 24-54 are appealed.

IV. STATUS OF AMENDMENTS

The claims were last amended in the Response and Amendment under 37 C.F.R. § 1.111 dated May 8, 2003. No amendment has been submitted subsequent to final rejection in the Final Office Action of July 24, 2003. A copy of the pending claims is attached in the Appendix to this Appeal Brief.

V. SUMMARY OF THE INVENTION

The invention provides a novel controlled release delivery system for administering more than one pharmaceutically effective agent. The delivery system is particularly useful for administering the enantiomers of chiral drugs, for example, the (+) and (-) enantiomers of tramadol. *See* Specification at page 3, line 27 – page 4, line 12.

The invention includes pharmaceutical compositions that provide an immediate release formulation of one enantiomer of a chiral compound, and a controlled release formulation of another enantiomer of a chiral compound. *See* Specification at page 16, lines 13-16. Controlled release is effected by a heteropolysaccharide and polysaccharide gum excipient known as TIMERx®. *See* Specification at page 15, lines 7-10 and Example 1, page 30, line 2 – page 35, line 5; *see also* “TIMERx” in U.S. Patent and Trademark Office, Trademark Database at www.uspto.gov. The application discloses particularly useful TIMERx® formulations containing xanthan gum and locust bean gum. *See* Specification at Example 1, page 30, line 2 – page 35, line 5. The claimed compositions are formulated for oral administration, for example, as a bi-layered tablet. *See* Specification at page 17, lines 22-29 and page 19, lines 15-16.

The pharmaceutical compositions of the invention are particularly advantageous for administering chiral drugs whose enantiomers are both pharmaceutically effective, but differ from one another, *e.g.*, in potency, pharmacokinetics, and/or safety profile. The claimed compositions allow for administration of both enantiomers at once, but with different delivery rates, thus enhancing the overall safety and efficacy of the chiral drug. *See* Specification at page 1, line 28 – page 3, line 6 and page 16, lines 13-16. Varying the amount and make-up of the

TIMERx® in a particular composition allows for manipulation of the drug release profile as desired. *See* Specification at Example 1, page 30, line 2 – page 35, line 5.

VI. ISSUE

Are claims 24-54 unobvious under 35 U.S.C. §103(a) over Gilbert et al., WO 98/40053 in combination with Baichwal et al., U.S. Patent No. 4,994,276?

VII. GROUPING OF CLAIMS

Claims 24-54 stand or fall together.

VIII. ARGUMENT

Claims 24-54 are unobvious under 35 U.S.C. §103(a) over Gilbert et al., WO 98/40053 (“Gilbert”) in combination with Baichwal et al., U.S. Patent No. 4,994,276 (“Baichwal”).

Gilbert teaches a dosage form having separate portions (*e.g.*, a bi-layer tablet), each portion containing one enantiomer of a chiral drug (*e.g.*, tramadol or warfarin). The enantiomers are released from the dosage form at different rates. Gilbert refers generally to employing conventional controlled release technology, but does not disclose or suggest a heteropolysaccharide and polysaccharide gum excipient. *See* Abstract and page 6, lines 30-35.

Baichwal teaches a heteropolysaccharide and polysaccharide gum excipient for controlled release delivery of a drug. *See* column 4, lines 8-54. However, Baichwal does not teach or suggest use of the disclosed excipient in a pharmaceutical composition containing both immediate release and controlled release formulations, or a pharmaceutical composition providing separate delivery rates for enantiomers of a chiral drug.

A *prima facie* case of obviousness over the combination of Gilbert and Baichwal has not been established. *Prima facie* obviousness requires some teaching, suggestion, or motivation to combine the references. The motivation to combine may come from the nature of the problem, but more often is found in the teachings of the cited references, or the knowledge of one of ordinary skill in the art that certain references are particularly important. The motivation to combine must not be based on improper hindsight in view of the claimed invention. *See In re Rouffet*, 149 F.3d 1350, 1355, 1358 (Fed. Cir. 1998). The showing of motivation to combine must be clear and particular, based on actual evidence, and not merely broad conclusory

statements regarding the teachings of multiple references. *See Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1125 (Fed. Cir. 2000) (citation omitted).

To prevent the use of hindsight based on the invention to defeat patentability ... the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art reference for combination in the manner claimed. ... [The examiner should] explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination. *In re Rouffet*, 49 F.3d at 1357-58.

Prior to Appellants' invention, there would have been no motivation for one of ordinary skill in the art to combine the teachings of Gilbert and Baichwal. Nothing in Baichwal suggests use of the disclosed sustained release excipient in two-part formulations providing separate delivery rates for enantiomers of a chiral drug. Similarly, nothing in Gilbert suggests use of the particular excipient of Baichwal in the disclosed two-part enantiomer formulations. The Examiner admitted that Gilbert does not teach a heteropolysaccharide and polysaccharide gum excipient, but asserted that Gilbert teaches the use of any conventional controlled release system to achieve the desired formulation, and that Baichwal provides one such conventional controlled release system. The Examiner argued further that one would be motivated to use the excipient of Baichwal in the formulations of Gilbert because Baichwal teaches that the disclosed excipient can be used with a wide variety of drugs and is easily compressible and inexpensive. *See* Final Office Action of July 24, 2003 at page 3, lines 4-7 and 16-22; page 4, lines 12-18; and page 5, lines 8-16.

The Examiner's conclusory statements do not provide sufficient evidence of motivation to combine to support a *prima facie* case of obviousness. In particular, the Examiner has not pointed out any specific reason why one of ordinary skill in the art, without the benefit of Appellants' disclosure, would select Baichwal's excipient from the thousands of known controlled release delivery systems for use in the two-part enantiomer formulations of Gilbert. Conclusory statements regarding the general advantages of Baichwal's excipient (*e.g.*, noting that it is inexpensive and can be used with a variety of drugs) do not suffice in view of the vast

number of available controlled release technologies, each of which may have their own particular advantages.

Appellants' response dated May 8, 2003 described a review of the PTO patent database at www.uspto.gov for patents issued from 1976 to May 6, 2003. Boolean searches of the database revealed **22,097** hits for the terms "controlled," "release," and "pharmaceutical"; **17,479** hits for the terms "sustained," "release," and "pharmaceutical"; and **11,214** hits for the terms "extended," and "release," and "pharmaceutical." In view of these search results, Appellants respectfully requested an explanation why one skilled in the art would be motivated to select Baichwal from among the more than 22,000 patents from 1976 to the present in the PTO database that describe conventional controlled-release technology. *See* Response and Amendment of May 8, 2003 at page 9, line 29 – page 10, line 8. In the Final Office Action of July 24, 2003, the Examiner failed to provide the requested explanation, instead simply dismissing Appellants' search results as "very broad and unpersuasive." To support this position, the Examiner stated that Appellants provided no evidence that all of the 22,097 references found by the search teach a controlled release system, and rather showed only that the three words appeared in the same reference. *See* Final Office Action at page 5, lines 17-22.

To address the Examiner's concern about the relevance of the identified references, Appellants performed an additional search of the PTO patent database on December 5, 2003, using the following search query: ("controlled release formulation" or "sustained release formulation" or "extended release formulation") and "pharmaceutical." Even this much more limited search, which mandates that the identified references disclose a controlled release formulation, revealed **2,061** hits. It should be remembered that these search results represent only U.S. patents issued since 1976, and the broader patent and scientific literature would certainly provide many more relevant search results. In view of these additional search results, Appellants again respectfully submit that a clear explanation should be provided why one of ordinary skill in the art would select the Baichwal reference from among the thousands of available references disclosing conventional controlled release technology. Without such an explanation, Appellants maintain that there simply would have been no motivation for one of ordinary skill in the art to select the sustained release excipient of Baichwal for use in the formulation described by Gilbert.

Gilbert itself expands on a large number of potential dosage forms, including oral, rectal, transdermal, ophthalmic, pulmonary, and injectable formulations of various types, *e.g.*, multi-particulates, multiple tablets, osmotic pumps, bi-layered tablets, transdermal patches, polymer implants, and aerosols. *See* page 5, line 31 – page 8, line 8. As discussed above, in describing these dosage forms, Gilbert refers to adjusting the rate of release of the enantiomers using “any conventional controlled-release mechanism, for instance, matrix (ie. erosion diffusion), coating, or osmotic.” *See, e.g.*, page 6, lines 9-14. In the Examples, Gilbert teaches controlled-release tablets and bi-layer tablets prepared with a particular controlled release excipient, namely, hydroxypropyl methyl cellulose (HPMC). *See* Examples 2-3, page 9, line 15 – page 10, line 17. The Examiner has not provided any reason why one of ordinary skill in the art would choose to prepare the formulations of Gilbert using any particular undisclosed conventional controlled release technology, rather than simply using HPMC, which Gilbert specifically teaches and exemplifies.

In sum, given the extremely large number of “conventional controlled release mechanisms,” and Gilbert’s exemplification of HPMC in particular, there would be no motivation to select the particular excipient of Baichwal for use in Gilbert’s two-part formulations. In the absence of any motivation to combine the cited references, Appellants’ claims are not obvious over Gilbert in view of Baichwal. *See In re Baird*, 16 F.3d 380, 383 (Fed. Cir. 1994) (claimed compound not obvious where cited reference teaches vast number of compounds and discloses typical or preferred compounds different from claimed compound, and thus does not suggest selection of claimed compound) (citing *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993) (claimed nucleic acid sequences not obvious over reference teaching almost infinite possibilities and not suggesting why one would choose the claimed sequences)); *In re Herschler*, 591 F.2d 693, 702 (C.C.P.A. 1979) (claimed combination of steroid and solvent DMSO not obvious where references teach general utility of DMSO as a solvent but there is no suggestion to choose DMSO from among countless numbers of solvents).

The U.S. Court of Appeals for the Federal Circuit has warned that it is improper to “use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.” *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). Furthermore, “the best defense against hindsight-based obviousness analysis is rigorous application of the requirement for a showing of a teaching or motivation to combine the prior art

references.” *Ecolochem, Inc. v. Southern California Edison Co.*, 277 F.3d 1361, 1371 (Fed. Cir. 2000) (citation omitted). With respect to Appellants’ claimed invention, there has been no showing of any motivation to combine the cited references, so *prima facie* obviousness has not been established, and the obviousness rejection is improper.

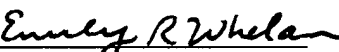
Accordingly, Appellants request that the Board of Patent Appeals and Interferences reverse the rejection under 35 U.S.C. § 103, and remand this case to the Examiner to withdraw the rejection and enter a Notice of Allowance.

IX. CONCLUSION

For the reasons advanced above, Appellants request that the Board of Patent Appeals and Interferences reverse the outstanding rejection, remand the application to the Examiner, and direct the Examiner to issue a Notice of Allowance.

Please deduct the \$165.00 fee for filing an appeal brief from our Deposit Account No. 08-0219. No other fees are believed to be due. However, please charge any payments due or credit any overpayments to our Deposit Account No. 08-0219.

Respectfully Submitted,


Emily R. Whelan
Registration No. 50,391

Dated: 12/16/03

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APPENDIX: Pending Claims

24. An orally administrable pharmaceutical composition comprising a therapeutically effective amount of an immediate release formulation comprising a (-) chiral compound enantiomer or a pharmaceutically acceptable salt thereof; and a controlled release formulation comprising a (+) chiral compound enantiomer or a pharmaceutically acceptable salt thereof and a heteropolysaccharide and polysaccharide gum excipient.

25. The composition of claim 24, wherein the ratio of the heteropolysaccharide and polysaccharide gum excipient to (+) chiral compound enantiomer or pharmaceutically acceptable salt thereof is between about 1:3 to 3:1.

26. The composition of claim 24, wherein the heteropolysaccharide and polysaccharide gum excipient comprises locust bean gum and xanthan gum.

27. The composition of claim 24, wherein the controlled release formulation comprises a (+) chiral compound enantiomer or a pharmaceutically acceptable salt thereof and a controlled release delivery system comprising 25% locust bean gum, 25% xanthan gum, 35% dextrose, 10% calcium sulfate, and 5% ethylcellulose.

28. The composition of claim 24, wherein the controlled release formulation comprises a (+) chiral compound enantiomer or a pharmaceutically acceptable salt thereof and a controlled release delivery system comprising 15% locust bean gum, 15% xanthan gum, 60% dextrose, and 10% calcium sulfate.

29. The composition of claim 24, wherein the composition is a bi-layered tablet.

30. The composition of claim 24, wherein the compound of the (+) and (-) chiral compound enantiomers is selected from the group consisting of warfarin, tramadol, mianserin, carvedilol, citalopram, dobutamine, aminoglutethimide, alfuzosin, celiprolol, cisapride, disopyramide, fenoldopam, flecainide, hydroxychloroquine, ifosfamide, labetolol, mexiletine, propafenone, tegafur, terazosin, thioctic acid, thiopental, and zalcopride.

31. The composition of claim 24, wherein, when measured by the USP type II dissolution method, the *in vitro* dissolution rate for the controlled release (CR) formulation and the immediate release (IR) formulation are:

Time (hours)	% CR Release	% IR Release
0	0%	0%
0.3	0-60 %	20-100 %
0.5	0-65 %	20-100 %
1.0	5-70 %	25-100 %
2.0	5-75 %	25-100 %
4.0	10-80 %	30-100 %
6.0	10-100 %	30-100 %
8.0	20-100 %	40-100 %
10.0	25-100 %	45-100 %
12.0	25-100 %	45-100 %
18.0	35-100 %	50-100 %
24.0	35-100 %	50-100 %.

32. The composition of claim 24, wherein the (+) chiral compound enantiomer and the (-) chiral compound enantiomer are present in the composition at different mass quantities.

33. The composition of claim 24, wherein the (+) chiral compound enantiomer and the (-) chiral compound enantiomer are present in the composition at a percent ratio selected from the following table:

(+) enantiomer	(-) enantiomer
2	1
3	1
4	1
5	1
10	1
1	2
1	3
1	4
1	5
1	10.

34. The composition of claim 24, wherein about 90% of the (+) chiral compound enantiomer and about 90% of the (-) chiral compound enantiomer are released within about 12 hours of administration.

35. The composition of claim 24, wherein when administered to a patient, the pharmaceutical composition provides the following percent of maximum (+) and (-) chiral compound enantiomer plasma concentrations:

Time (hours)	(+) Enantiomer	(-) Enantiomer
0	0%	0%
0.3	0-60 %	0-100 %
0.5	0-65 %	0-100 %
1.0	5-70 %	25-100 %
2.0	5-75 %	25-100 %
4.0	10-80 %	30-100 %
6.0	20-100 %	30-100 %
8.0	20-100 %	20-100 %
10.0	20-100 %	20-100 %
12.0	10-100 %	0-90 %
18.0	0-80 %	0-80 %
24.0	0-80 %	0-80 %.

36. The composition of claim 24, wherein, when administered to a patient, the pharmaceutical composition provides the following percent of maximum (+) and (-) chiral drug enantiomer plasma concentrations:

Time (hours)	(+) Enantiomer	(-) Enantiomer
0	0%	0%
0.3	0-40 %	0-100 %
0.5	0-45 %	0-100 %
1.0	5-50 %	25-100 %
2.0	5-55 %	25-100 %
4.0	10-80 %	30-100 %

6.0	20-100 %	30-100 %
8.0	20-100 %	20-100 %
10.0	10-100 %	20-100 %
12.0	0-80 %	10-90 %
18.0	0-80 %	0-80 %
24.0	0-80 %	0-80 %.

37. The composition of claim 24, wherein the compound of the (+) and (-) chiral compound enantiomers is tramadol.

38. The composition of claim 37, wherein the (+) tramadol enantiomer and the (-) tramadol enantiomer are present in the composition at a percent ratio of 3:1.

39. The composition of claim 37, wherein the (+) tramadol enantiomer and the (-) tramadol enantiomer are present in the composition at a percent ratio of 2:1.

40. An orally administrable pharmaceutical composition comprising a therapeutically effective amount of an immediate release formulation comprising a (+) chiral compound enantiomer or a pharmaceutically acceptable salt thereof; and a controlled release formulation comprising a (-) chiral compound enantiomer or a pharmaceutically acceptable salt thereof and a heteropolysaccharide and polysaccharide gum excipient.

41. The composition of claim 40, wherein the ratio of the heteropolysaccharide and polysaccharide gum excipient to (-) chiral compound enantiomer or pharmaceutically acceptable salt thereof is between about 1:3 to 3:1.

42. The composition of claim 40, wherein the heteropolysaccharide and polysaccharide gum excipient comprises locust bean gum and xanthan gum.

43. The composition of claim 40, wherein the controlled release formulation comprises a (-) chiral compound enantiomer or a pharmaceutically acceptable salt thereof and a controlled release delivery system comprising 25% locust bean gum, 25% xanthan gum, 35% dextrose, 10% calcium sulfate, and 5% ethylcellulose.

44. The composition of claim 40, wherein the controlled release formulation comprises a (-) chiral compound enantiomer or a pharmaceutically acceptable salt thereof and a controlled release delivery system comprising 15% locust bean gum, 15% xanthan gum, 60% dextrose, and 10% calcium sulfate.

45. The composition of claim 40, wherein the composition is a bi-layered tablet.

46. The composition of claim 40, wherein the compound of the (+) and (-) chiral compound enantiomers is selected from the group consisting of warfarin, tramadol, mianserin, carvedilol, citalopram, dobutamine, aminoglutethimide, alfuzosin, celiprolol, cisapride, disopyramide, fenoldopam, flecainide, hydroxychloroquine, ifosfamide, labetolol, mexiletine, propafenone, tegafur, terazosin, thioctic acid, thiopental, and zacopride.

47. The composition of claim 40, wherein, when measured by the USP type II dissolution method, the *in vitro* dissolution rate for the controlled release (CR) formulation and the immediate release (IR) formulation are:

Time (hours)	% CR Release	% IR Release
0	0%	0%

0.3	0-60 %	20-100 %
0.5	0-65 %	20-100 %
1.0	5-70 %	25-100 %
2.0	5-75 %	25-100 %
4.0	10-80 %	30-100 %
6.0	10-100 %	30-100 %
8.0	20-100 %	40-100 %
10.0	25-100 %	45-100 %
12.0	25-100 %	45-100 %
18.0	35-100 %	50-100 %
24.0	35-100 %	50-100 %.

48. The composition of claim 40, wherein the (+) chiral compound enantiomer and the (-) chiral compound enantiomer are present in the composition at different mass quantities.

49. The composition of claim 40, wherein the (+) chiral compound enantiomer and the (-) chiral compound enantiomer are present in the composition at a percent ratio selected from the following table:

(+) enantiomer	(-) enantiomer
2	1
3	1
4	1
5	1
10	1

1	2
1	3
1	4
1	5
1	10.

50. The composition of claim 40, wherein about 90% of the (+) chiral compound enantiomer and about 90% of the (-) chiral compound enantiomer are released within about 12 hours of administration.

51. The composition of claim 40, wherein when administered to a patient, the pharmaceutical composition provides the following percent of maximum (+) and (-) chiral compound enantiomer plasma concentrations:

Time (hours)	(+) Enantiomer	(-) Enantiomer
0	0%	0%
0.3	0-60 %	0-100 %
0.5	0-65 %	0-100 %
1.0	5-70 %	25-100 %
2.0	5-75 %	25-100 %
4.0	10-80 %	30-100 %
6.0	20-100 %	30-100 %
8.0	20-100 %	20-100 %
10.0	20-100 %	20-100 %
12.0	10-100 %	0-90 %

18.0	0-80 %	0-80 %
24.0	0-80 %	0-80 %.

52. The composition of claim 40, wherein, when administered to a patient, the pharmaceutical composition provides the following percent of maximum (+) and (-) chiral drug enantiomer plasma concentrations:

Time (hours)	(+) Enantiomer	(-) Enantiomer
0	0%	0%
0.3	0-40 %	0-100 %
0.5	0-45 %	0-100 %
1.0	5-50 %	25-100 %
2.0	5-55 %	25-100 %
4.0	10-80 %	30-100 %
6.0	20-100 %	30-100 %
8.0	20-100 %	20-100 %
10.0	10-100 %	20-100 %
12.0	0-80 %	10-90 %
18.0	0-80 %	0-80 %
24.0	0-80 %	0-80 %.

53. The composition of claim 40, wherein the compound is tramadol.

54. A bi-layered, orally administrable tablet comprising:

- (a) a controlled release formulation comprising about 5.4% by weight (+) tramadol or a pharmaceutically acceptable salt thereof; about 37.7% by weight of a controlled release

delivery system; about 16.2% by weight silicified microcrystalline cellulose; and about 0.6% by weight magnesium stearate; wherein the controlled release delivery system comprises 25% locust bean gum, 25% xanthan gum, 35% dextrose, 10% calcium sulfate, and 5% ethylcellulose; and

(b) an immediate release formulation comprising about 16.2% by weight (-) tramadol or a pharmaceutically acceptable salt thereof; about 10.8% by weight silicified microcrystalline cellulose; about 10.8% lactose fast flow; about 2.2% sodium starch glycolate and about 0.3 % by weight magnesium stearate;

wherein the % by weight is based on the weight of the bi-layered, orally administrable tablet.



PATENT

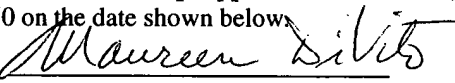
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Liu et al.)	Examiner:	R. Joynes
)		
Serial No.:	09/970,020)	Art Unit:	1615
)		
Filed:	October 3, 2001)	Confirmation No.:	8697
)		
Entitled:	Developing A Delivery System For Multi-Pharmaceutical Active Materials at Various Release Rates)	Atty. Docket No.:	107223-139 US
)		

CERTIFICATION UNDER 37 C.F.R. § 1.10

I hereby certify that the attached papers are being deposited with the United States Postal Service as "Express Mail Post Office to Addressee" Mailing Label No. **EV207558766US** addressed to: **Mail Stop Appeal Brief - Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450** on the date shown below:

December 16, 2003
Date of Signature and of Mailing


Maureen DiVito

APPEAL BRIEF UNDER 37 C.F.R. § 1.192

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an Appeal Brief pursuant to the Notice of Appeal filed on October 23, 2003, appealing the rejection of claims 24-54 in the Final Office Action of July 24, 2003. This Brief is being filed in triplicate.

I. REAL PARTY IN INTEREST

The real party in interest is Penwest Pharmaceuticals Co., the assignee of the present application.

II. RELATED APPEALS AND INTERFERENCES

The Appellants, the Appellants' legal representatives, and the Assignee are not aware of any pending appeal or interference that would directly affect, be directly affected by, or have a bearing on the Board's decision in this appeal.

III. STATUS OF THE CLAIMS

Claims 24-54 are pending in the application, and are finally rejected. Claims 1-23 were canceled during prosecution. Claims 24-54 are appealed.

IV. STATUS OF AMENDMENTS

The claims were last amended in the Response and Amendment under 37 C.F.R. § 1.111 dated May 8, 2003. No amendment has been submitted subsequent to final rejection in the Final Office Action of July 24, 2003. A copy of the pending claims is attached in the Appendix to this Appeal Brief.

V. SUMMARY OF THE INVENTION

The invention provides a novel controlled release delivery system for administering more than one pharmaceutically effective agent. The delivery system is particularly useful for administering the enantiomers of chiral drugs, for example, the (+) and (-) enantiomers of tramadol. *See* Specification at page 3, line 27 – page 4, line 12.

The invention includes pharmaceutical compositions that provide an immediate release formulation of one enantiomer of a chiral compound, and a controlled release formulation of another enantiomer of a chiral compound. *See* Specification at page 16, lines 13-16. Controlled release is effected by a heteropolysaccharide and polysaccharide gum excipient known as TIMERx®. *See* Specification at page 15, lines 7-10 and Example 1, page 30, line 2 – page 35, line 5; *see also* “TIMERx” in U.S. Patent and Trademark Office, Trademark Database at www.uspto.gov. The application discloses particularly useful TIMERx® formulations containing xanthan gum and locust bean gum. *See* Specification at Example 1, page 30, line 2 – page 35, line 5. The claimed compositions are formulated for oral administration, for example, as a bi-layered tablet. *See* Specification at page 17, lines 22-29 and page 19, lines 15-16.

The pharmaceutical compositions of the invention are particularly advantageous for administering chiral drugs whose enantiomers are both pharmaceutically effective, but differ from one another, *e.g.*, in potency, pharmacokinetics, and/or safety profile. The claimed compositions allow for administration of both enantiomers at once, but with different delivery rates, thus enhancing the overall safety and efficacy of the chiral drug. *See* Specification at page 1, line 28 – page 3, line 6 and page 16, lines 13-16. Varying the amount and make-up of the

TIMERx® in a particular composition allows for manipulation of the drug release profile as desired. *See* Specification at Example 1, page 30, line 2 – page 35, line 5.

VI. ISSUE

Are claims 24-54 unobvious under 35 U.S.C. §103(a) over Gilbert et al., WO 98/40053 in combination with Baichwal et al., U.S. Patent No. 4,994,276?

VII. GROUPING OF CLAIMS

Claims 24-54 stand or fall together.

VIII. ARGUMENT

Claims 24-54 are unobvious under 35 U.S.C. §103(a) over Gilbert et al., WO 98/40053 (“Gilbert”) in combination with Baichwal et al., U.S. Patent No. 4,994,276 (“Baichwal”).

Gilbert teaches a dosage form having separate portions (*e.g.*, a bi-layer tablet), each portion containing one enantiomer of a chiral drug (*e.g.*, tramadol or warfarin). The enantiomers are released from the dosage form at different rates. Gilbert refers generally to employing conventional controlled release technology, but does not disclose or suggest a heteropolysaccharide and polysaccharide gum excipient. *See* Abstract and page 6, lines 30-35.

Baichwal teaches a heteropolysaccharide and polysaccharide gum excipient for controlled release delivery of a drug. *See* column 4, lines 8-54. However, Baichwal does not teach or suggest use of the disclosed excipient in a pharmaceutical composition containing both immediate release and controlled release formulations, or a pharmaceutical composition providing separate delivery rates for enantiomers of a chiral drug.

A prima facie case of obviousness over the combination of Gilbert and Baichwal has not been established. *Prima facie* obviousness requires some teaching, suggestion, or motivation to combine the references. The motivation to combine may come from the nature of the problem, but more often is found in the teachings of the cited references, or the knowledge of one of ordinary skill in the art that certain references are particularly important. The motivation to combine must not be based on improper hindsight in view of the claimed invention. *See In re Rouffet*, 149 F.3d 1350, 1355, 1358 (Fed. Cir. 1998). The showing of motivation to combine must be clear and particular, based on actual evidence, and not merely broad conclusory

statements regarding the teachings of multiple references. *See Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1125 (Fed. Cir. 2000) (citation omitted).

To prevent the use of hindsight based on the invention to defeat patentability ... the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art reference for combination in the manner claimed. ... [The examiner should] explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination. *In re Rouffet*, 49 F.3d at 1357-58.

Prior to Appellants' invention, there would have been no motivation for one of ordinary skill in the art to combine the teachings of Gilbert and Baichwal. Nothing in Baichwal suggests use of the disclosed sustained release excipient in two-part formulations providing separate delivery rates for enantiomers of a chiral drug. Similarly, nothing in Gilbert suggests use of the particular excipient of Baichwal in the disclosed two-part enantiomer formulations. The Examiner admitted that Gilbert does not teach a heteropolysaccharide and polysaccharide gum excipient, but asserted that Gilbert teaches the use of any conventional controlled release system to achieve the desired formulation, and that Baichwal provides one such conventional controlled release system. The Examiner argued further that one would be motivated to use the excipient of Baichwal in the formulations of Gilbert because Baichwal teaches that the disclosed excipient can be used with a wide variety of drugs and is easily compressible and inexpensive. *See* Final Office Action of July 24, 2003 at page 3, lines 4-7 and 16-22; page 4, lines 12-18; and page 5, lines 8-16.

The Examiner's conclusory statements do not provide sufficient evidence of motivation to combine to support a *prima facie* case of obviousness. In particular, the Examiner has not pointed out any specific reason why one of ordinary skill in the art, without the benefit of Appellants' disclosure, would select Baichwal's excipient from the thousands of known controlled release delivery systems for use in the two-part enantiomer formulations of Gilbert. Conclusory statements regarding the general advantages of Baichwal's excipient (*e.g.*, noting that it is inexpensive and can be used with a variety of drugs) do not suffice in view of the vast

number of available controlled release technologies, each of which may have their own particular advantages.

Appellants' response dated May 8, 2003 described a review of the PTO patent database at www.uspto.gov for patents issued from 1976 to May 6, 2003. Boolean searches of the database revealed **22,097** hits for the terms "controlled," "release," and "pharmaceutical"; **17,479** hits for the terms "sustained," "release," and "pharmaceutical"; and **11,214** hits for the terms "extended," and "release," and "pharmaceutical." In view of these search results, Appellants respectfully requested an explanation why one skilled in the art would be motivated to select Baichwal from among the more than 22,000 patents from 1976 to the present in the PTO database that describe conventional controlled-release technology. *See* Response and Amendment of May 8, 2003 at page 9, line 29 – page 10, line 8. In the Final Office Action of July 24, 2003, the Examiner failed to provide the requested explanation, instead simply dismissing Appellants' search results as "very broad and unpersuasive." To support this position, the Examiner stated that Appellants provided no evidence that all of the 22,097 references found by the search teach a controlled release system, and rather showed only that the three words appeared in the same reference. *See* Final Office Action at page 5, lines 17-22.

To address the Examiner's concern about the relevance of the identified references, Appellants performed an additional search of the PTO patent database on December 5, 2003, using the following search query: ("controlled release formulation" or "sustained release formulation" or "extended release formulation") and "pharmaceutical." Even this much more limited search, which mandates that the identified references disclose a controlled release formulation, revealed **2,061** hits. It should be remembered that these search results represent only U.S. patents issued since 1976, and the broader patent and scientific literature would certainly provide many more relevant search results. In view of these additional search results, Appellants again respectfully submit that a clear explanation should be provided why one of ordinary skill in the art would select the Baichwal reference from among the thousands of available references disclosing conventional controlled release technology. Without such an explanation, Appellants maintain that there simply would have been no motivation for one of ordinary skill in the art to select the sustained release excipient of Baichwal for use in the formulation described by Gilbert.

Gilbert itself expands on a large number of potential dosage forms, including oral, rectal, transdermal, ophthalmic, pulmonary, and injectable formulations of various types, *e.g.*, multi-particulates, multiple tablets, osmotic pumps, bi-layered tablets, transdermal patches, polymer implants, and aerosols. *See* page 5, line 31 – page 8, line 8. As discussed above, in describing these dosage forms, Gilbert refers to adjusting the rate of release of the enantiomers using “any conventional controlled-release mechanism, for instance, matrix (ie. erosion diffusion), coating, or osmotic.” *See, e.g.*, page 6, lines 9-14. In the Examples, Gilbert teaches controlled-release tablets and bi-layer tablets prepared with a particular controlled release excipient, namely, hydroxypropyl methyl cellulose (HPMC). *See* Examples 2-3, page 9, line 15 – page 10, line 17. The Examiner has not provided any reason why one of ordinary skill in the art would choose to prepare the formulations of Gilbert using any particular undisclosed conventional controlled release technology, rather than simply using HPMC, which Gilbert specifically teaches and exemplifies.

In sum, given the extremely large number of “conventional controlled release mechanisms,” and Gilbert’s exemplification of HPMC in particular, there would be no motivation to select the particular excipient of Baichwal for use in Gilbert’s two-part formulations. In the absence of any motivation to combine the cited references, Appellants’ claims are not obvious over Gilbert in view of Baichwal. *See In re Baird*, 16 F.3d 380, 383 (Fed. Cir. 1994) (claimed compound not obvious where cited reference teaches vast number of compounds and discloses typical or preferred compounds different from claimed compound, and thus does not suggest selection of claimed compound) (citing *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993) (claimed nucleic acid sequences not obvious over reference teaching almost infinite possibilities and not suggesting why one would choose the claimed sequences)); *In re Herschler*, 591 F.2d 693, 702 (C.C.P.A. 1979) (claimed combination of steroid and solvent DMSO not obvious where references teach general utility of DMSO as a solvent but there is no suggestion to choose DMSO from among countless numbers of solvents).

The U.S. Court of Appeals for the Federal Circuit has warned that it is improper to “use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.” *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). Furthermore, “the best defense against hindsight-based obviousness analysis is rigorous application of the requirement for a showing of a teaching or motivation to combine the prior art

references.” *Ecolochem, Inc. v. Southern California Edison Co.*, 277 F.3d 1361, 1371 (Fed. Cir. 2000) (citation omitted). With respect to Appellants’ claimed invention, there has been no showing of any motivation to combine the cited references, so *prima facie* obviousness has not been established, and the obviousness rejection is improper.

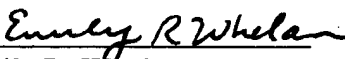
Accordingly, Appellants request that the Board of Patent Appeals and Interferences reverse the rejection under 35 U.S.C. § 103, and remand this case to the Examiner to withdraw the rejection and enter a Notice of Allowance.

IX. CONCLUSION

For the reasons advanced above, Appellants request that the Board of Patent Appeals and Interferences reverse the outstanding rejection, remand the application to the Examiner, and direct the Examiner to issue a Notice of Allowance.

Please deduct the \$165.00 fee for filing an appeal brief from our Deposit Account No. 08-0219. No other fees are believed to be due. However, please charge any payments due or credit any overpayments to our Deposit Account No. 08-0219.

Respectfully Submitted,



Emily R. Whelan
Registration No. 50,391

Dated: 12/16/03

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APPENDIX: Pending Claims

24. An orally administrable pharmaceutical composition comprising a therapeutically effective amount of an immediate release formulation comprising a (-) chiral compound enantiomer or a pharmaceutically acceptable salt thereof; and a controlled release formulation comprising a (+) chiral compound enantiomer or a pharmaceutically acceptable salt thereof and a heteropolysaccharide and polysaccharide gum excipient.

25. The composition of claim 24, wherein the ratio of the heteropolysaccharide and polysaccharide gum excipient to (+) chiral compound enantiomer or pharmaceutically acceptable salt thereof is between about 1:3 to 3:1.

26. The composition of claim 24, wherein the heteropolysaccharide and polysaccharide gum excipient comprises locust bean gum and xanthan gum.

27. The composition of claim 24, wherein the controlled release formulation comprises a (+) chiral compound enantiomer or a pharmaceutically acceptable salt thereof and a controlled release delivery system comprising 25% locust bean gum, 25% xanthan gum, 35% dextrose, 10% calcium sulfate, and 5% ethylcellulose.

28. The composition of claim 24, wherein the controlled release formulation comprises a (+) chiral compound enantiomer or a pharmaceutically acceptable salt thereof and a controlled release delivery system comprising 15% locust bean gum, 15% xanthan gum, 60% dextrose, and 10% calcium sulfate.

29. The composition of claim 24, wherein the composition is a bi-layered tablet.

30. The composition of claim 24, wherein the compound of the (+) and (-) chiral compound enantiomers is selected from the group consisting of warfarin, tramadol, mianserin, carvedilol, citalopram, dobutamine, aminoglutethimide, alfuzosin, celiprolol, cisapride, disopyramide, fenoldopam, flecainide, hydroxychloroquine, ifosfamide, labetolol, mexiletine, propafenone, tegafur, terazosin, thiocetic acid, thiopental, and zacopride.

31. The composition of claim 24, wherein, when measured by the USP type II dissolution method, the *in vitro* dissolution rate for the controlled release (CR) formulation and the immediate release (IR) formulation are:

Time (hours)	% CR Release	% IR Release
0	0%	0%
0.3	0-60 %	20-100 %
0.5	0-65 %	20-100 %
1.0	5-70 %	25-100 %
2.0	5-75 %	25-100 %
4.0	10-80 %	30-100 %
6.0	10-100 %	30-100 %
8.0	20-100 %	40-100 %
10.0	25-100 %	45-100 %
12.0	25-100 %	45-100 %
18.0	35-100 %	50-100 %
24.0	35-100 %	50-100 %.

32. The composition of claim 24, wherein the (+) chiral compound enantiomer and the (-) chiral compound enantiomer are present in the composition at different mass quantities.

33. The composition of claim 24, wherein the (+) chiral compound enantiomer and the (-) chiral compound enantiomer are present in the composition at a percent ratio selected from the following table:

(+) enantiomer	(-) enantiomer
2	1
3	1
4	1
5	1
10	1
1	2
1	3
1	4
1	5
1	10.

34. The composition of claim 24, wherein about 90% of the (+) chiral compound enantiomer and about 90% of the (-) chiral compound enantiomer are released within about 12 hours of administration.

35. The composition of claim 24, wherein when administered to a patient, the pharmaceutical composition provides the following percent of maximum (+) and (-) chiral compound enantiomer plasma concentrations:

Time (hours)	(+) Enantiomer	(-) Enantiomer
0	0%	0%
0.3	0-60 %	0-100 %
0.5	0-65 %	0-100 %
1.0	5-70 %	25-100 %
2.0	5-75 %	25-100 %
4.0	10-80 %	30-100 %
6.0	20-100 %	30-100 %
8.0	20-100 %	20-100 %
10.0	20-100 %	20-100 %
12.0	10-100 %	0-90 %
18.0	0-80 %	0-80 %
24.0	0-80 %	0-80 %.

36. The composition of claim 24, wherein, when administered to a patient, the pharmaceutical composition provides the following percent of maximum (+) and (-) chiral drug enantiomer plasma concentrations:

Time (hours)	(+) Enantiomer	(-) Enantiomer
0	0%	0%
0.3	0-40 %	0-100 %
0.5	0-45 %	0-100 %
1.0	5-50 %	25-100 %
2.0	5-55 %	25-100 %
4.0	10-80 %	30-100 %

6.0	20-100 %	30-100 %
8.0	20-100 %	20-100 %
10.0	10-100 %	20-100 %
12.0	0-80 %	10-90 %
18.0	0-80 %	0-80 %
24.0	0-80 %	0-80 %.

37. The composition of claim 24, wherein the compound of the (+) and (-) chiral compound enantiomers is tramadol.

38. The composition of claim 37, wherein the (+) tramadol enantiomer and the (-) tramadol enantiomer are present in the composition at a percent ratio of 3:1.

39. The composition of claim 37, wherein the (+) tramadol enantiomer and the (-) tramadol enantiomer are present in the composition at a percent ratio of 2:1.

40. An orally administrable pharmaceutical composition comprising a therapeutically effective amount of an immediate release formulation comprising a (+) chiral compound enantiomer or a pharmaceutically acceptable salt thereof; and a controlled release formulation comprising a (-) chiral compound enantiomer or a pharmaceutically acceptable salt thereof and a heteropolysaccharide and polysaccharide gum excipient.

41. The composition of claim 40, wherein the ratio of the heteropolysaccharide and polysaccharide gum excipient to (-) chiral compound enantiomer or pharmaceutically acceptable salt thereof is between about 1:3 to 3:1.

42. The composition of claim 40, wherein the heteropolysaccharide and polysaccharide gum excipient comprises locust bean gum and xanthan gum.

43. The composition of claim 40, wherein the controlled release formulation comprises a (-) chiral compound enantiomer or a pharmaceutically acceptable salt thereof and a controlled release delivery system comprising 25% locust bean gum, 25% xanthan gum, 35% dextrose, 10% calcium sulfate, and 5% ethylcellulose.

44. The composition of claim 40, wherein the controlled release formulation comprises a (-) chiral compound enantiomer or a pharmaceutically acceptable salt thereof and a controlled release delivery system comprising 15% locust bean gum, 15% xanthan gum, 60% dextrose, and 10% calcium sulfate.

45. The composition of claim 40, wherein the composition is a bi-layered tablet.

46. The composition of claim 40, wherein the compound of the (+) and (-) chiral compound enantiomers is selected from the group consisting of warfarin, tramadol, mianserin, carvedilol, citalopram, dobutamine, aminoglutethimide, alfuzosin, celiprolol, cisapride, disopyramide, fenoldopam, flecainide, hydroxychloroquine, ifosfamide, labetolol, mexiletine, propafenone, tegafur, terazosin, thiocetic acid, thiopental, and zacopride.

47. The composition of claim 40, wherein, when measured by the USP type II dissolution method, the *in vitro* dissolution rate for the controlled release (CR) formulation and the immediate release (IR) formulation are:

Time (hours)	% CR Release	% IR Release
0	0%	0%

0.3	0-60 %	20-100 %
0.5	0-65 %	20-100 %
1.0	5-70 %	25-100 %
2.0	5-75 %	25-100 %
4.0	10-80 %	30-100 %
6.0	10-100 %	30-100 %
8.0	20-100 %	40-100 %
10.0	25-100 %	45-100 %
12.0	25-100 %	45-100 %
18.0	35-100 %	50-100 %
24.0	35-100 %	50-100 %.

48. The composition of claim 40, wherein the (+) chiral compound enantiomer and the (-) chiral compound enantiomer are present in the composition at different mass quantities.

49. The composition of claim 40, wherein the (+) chiral compound enantiomer and the (-) chiral compound enantiomer are present in the composition at a percent ratio selected from the following table:

(+) enantiomer	(-) enantiomer
2	1
3	1
4	1
5	1
10	1

1	2
1	3
1	4
1	5
1	10.

50. The composition of claim 40, wherein about 90% of the (+) chiral compound enantiomer and about 90% of the (-) chiral compound enantiomer are released within about 12 hours of administration.

51. The composition of claim 40, wherein when administered to a patient, the pharmaceutical composition provides the following percent of maximum (+) and (-) chiral compound enantiomer plasma concentrations:

Time (hours)	(+) Enantiomer	(-) Enantiomer
0	0%	0%
0.3	0-60 %	0-100 %
0.5	0-65 %	0-100 %
1.0	5-70 %	25-100 %
2.0	5-75 %	25-100 %
4.0	10-80 %	30-100 %
6.0	20-100 %	30-100 %
8.0	20-100 %	20-100 %
10.0	20-100 %	20-100 %
12.0	10-100 %	0-90 %

18.0	0-80 %	0-80 %
24.0	0-80 %	0-80 %.

52. The composition of claim 40, wherein, when administered to a patient, the pharmaceutical composition provides the following percent of maximum (+) and (-) chiral drug enantiomer plasma concentrations:

Time (hours)	(+) Enantiomer	(-) Enantiomer
0	0%	0%
0.3	0-40 %	0-100 %
0.5	0-45 %	0-100 %
1.0	5-50 %	25-100 %
2.0	5-55 %	25-100 %
4.0	10-80 %	30-100 %
6.0	20-100 %	30-100 %
8.0	20-100 %	20-100 %
10.0	10-100 %	20-100 %
12.0	0-80 %	10-90 %
18.0	0-80 %	0-80 %
24.0	0-80 %	0-80 %.

53. The composition of claim 40, wherein the compound is tramadol.

54. A bi-layered, orally administrable tablet comprising:

(a) a controlled release formulation comprising about 5.4% by weight (+) tramadol or a pharmaceutically acceptable salt thereof; about 37.7% by weight of a controlled release

delivery system; about 16.2% by weight silicified microcrystalline cellulose; and about 0.6% by weight magnesium stearate; wherein the controlled release delivery system comprises 25% locust bean gum, 25% xanthan gum, 35% dextrose, 10% calcium sulfate, and 5% ethylcellulose; and

(b) an immediate release formulation comprising about 16.2% by weight (-) tramadol or a pharmaceutically acceptable salt thereof; about 10.8% by weight silicified microcrystalline cellulose; about 10.8% lactose fast flow; about 2.2% sodium starch glycolate and about 0.3 % by weight magnesium stearate;

wherein the % by weight is based on the weight of the bi-layered, orally administrable tablet.

